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ON THE CHEAPER
ALKALOIDS OF THE CINCHONAS.

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ON THE CHEAPER

ALKALOIDS OF THE CINCHONAS.

THE Cinchona Barks are, without doubt, the most precious contribution of the New World to the Materia Medica of the Old. Their entire control over all the forms of Intermittent Fever was early ascertained, and remains undisputed and unrivaled. Three varieties of the Bark have usually been distinguished in commerce, viz: the Pale or Gray Bark, or the Crown Bark of Loxa; the Yellow or Calisaya Bark; and the Red Bark. For more than a century after the Peruvian Bark came into use it was procured almost exclusively from Loxa and the neighboring provinces.

It was this variety—the Pale or Gray Bark—in all probability, the success of which established the reputation of Peruvian Bark as an anti-periodic.

The Yellow or Calisaya Bark appears to have come later into notice, and to have been generally preferred on account of its greater bitterness and stronger taste.

The Red Bark is stronger and more astringent than either of the others. Humboldt says that “in intermittent fevers the *C. Condaminea*, (*the Crown Bark of Loxa*,) and *C. Lancifolia* (*the Calisaya Bark*,) are preferable to the others; while in diseases of the muscles and purulent ulcers *C. Oblongifolia* (*the Red*

Bark) is more fitted, and the milder *C. Cordifolia* (*the Gray Huanuco Bark*) is adapted for convalescents."

When Humboldt wrote the above, the trees producing the several commercial varieties of Bark had not been fully identified, but the barks mentioned in the parenthesis are those which he believed to be the products of the species named by him.

In this country the best Red Bark has always been regarded as the bark most to be relied upon in obstinate intermittents.

It was in the year 1803 that Dr. Duncan, of Edinburgh, announced the existence of a peculiar proximate principle in Peruvian Bark which he called Cinchonine. Dr. Gomez, a Portuguese physician, followed up these researches in the year 1810, and obtained the Cinchonine in a crystalline form, but without suspecting its alkaline nature. In 1806 Vauquelin undertook the chemical examination of the Cinchonas, and isolated the Kinic acid.

Little more was added to our knowledge respecting them, till the brilliant discoveries of Pelletier and Caventou were made known in 1820.

They began their researches by the examination of the Gray Bark. "Kina Losas, *Cinchona Condaminea*, generally regarded," say they, "as the type of the various barks." Repeating the experiments of Dr. Gomez, with their own greater chemical skill, they ascertained the alkaline nature of Cinchonina, and most of its properties, prepared its sulphate and many other of its salts, and proved that it existed in the bark combined with Kinic acid.

They next directed their attention to the Yellow Bark. "*Cinchona Cordifolia*," as they call it, and

were rewarded by the discovery of the new Alkali Quinia, the properties and combinations of which they investigated, but without succeeding in obtaining the alkali itself in a crystalline form.

They completed their labours by the analysis of the Red Bark, "*Cinchona Oblongifolia*," in which they discovered both alkalies to exist.

"If," say they, "we have established that the active principle of the Cinchonas resides in a salifiable base, we can explain how it is that the gray and yellow Cinchonas present shades of difference in their medicinal properties. As to the Red Bark, it is the best of the Cinchonas, since it unites the two principles, and combines them in the greatest proportions."

When subsequent analysis discovered that these alkalies differed in composition by only an atom of oxygen, the presumption as to their equal curative powers, derived from the fact that they existed separately, one in the pale, and one in the yellow bark, and combined in the red, all which barks were celebrated for their anti-febrile virtues, seemed to amount to certainty.

Perhaps it is not difficult to explain how it happened, that one of them, the Quinia, has come into universal use, to the almost total neglect of the other.

These distinguished chemists were naturally anxious to test the virtues of the new alkalies, and they submitted specimens of the sulphates of both to the principal physicians of Paris for trial.

Their attention was principally directed to the effects of the Sulphate of Quinia, which was more readily attainable and in greater quantities than the Cinchonina from the barks then in use.

Out of twenty cases reported—fourteen by Dr Chomel and six by Dr. Double—the Sulphate of Cinchonia was administered only in one, and that of Quinia in all the others. The success of the latter was so great that it became, from that time, the universal remedy for intermittent fever. The medical profession was satisfied with its powers, and did not care to inquire into the virtues of the Cinchonia. Time and experience have only added to the reputation of the Quinia, and it is unnecessary here to enter into any details respecting its properties. The object of this memoir is to call attention to other preparations from the Cinchonas.

Although the single trial of Dr. Chomel “did not fully realize his expectations,” and the further use of Cinchonia was, for the time being, prematurely abandoned, there is no reason to doubt that it is equally efficacious with the Quinia. The patient on whom he tried it “had been suffering with the disease for two months, in the quotidian form, and also had great enlargement of the spleen; at first only six grains of the Cinchonia were administered during the apyrexia, but as this failed to check the disease, on the following day twenty grains were administered, with the effect of completely arresting the paroxysms. Upon reducing the dose, however, it appears that the patient soon relapsed, and was not permanently cured until twenty-four grains were given during the intermission. When we bear in mind that the above case had been of long duration, and was complicated with visceral enlargement, it is by no means surprising that the disease was not checked by small doses of Cinchonia at the first effort, or that it should even

have recurred after it had once been arrested by larger doses; for, under similar circumstances, it is well known that the same difficulties will often occur under the use of Quinia, or any other treatment that may be instituted. And yet there is good reason to believe that the partial want of success in this single instance has had much to do in establishing the common opinion that Cinchonia is less energetic than Quinia, and consequently requires to be given in a stronger dose.

A more thorough and impartial trial of this important remedy was, however, made by Dr. Bally, in 1825. He gave the sulphate in twenty-seven cases of intermittent fever; and, although only six or eight grains were administered during the intermissions, he succeeded in promptly checking twenty-five of the cases, sixteen of which were of the tertian, and nine of the quotidian type, the average duration of the treatment being only four days. The remaining two cases were quartans, and these were checked quite as promptly as this most obstinate form generally is, by Quinia or any other therapeutic agent; in one instance the disease lasted only two days, and in the other it was permanently checked by the end of one week. From these observations, the above-named author concluded that the Sulphate of Cinchonia arrested acute paroxysmal affections with great promptitude, and that but a moderate dose was necessary for this result; he also inferred that it was less irritating, and that it might, therefore, be more generally administered than the same salt of quinia; he was even disposed to ascribe many of the cures usually attributed to this last-named substance to the well-known fact that it was no un-

common thing to adulterate Quinia with Cinchonia. In the *Dictionnaire Universel de Matière Médicale*, par Mérat et De Lens, allusion is made to numerous instances in which the Cinchonia had been successfully used by French and Italian physicians; amongst these may be mentioned Dufour, Petroz, Potier, Mariani, and Bleyne; by all of whom it was fully shown that Cinchonia was at least as efficacious as Quinia. In confirmation of the same views, we also find it stated, in *Christison's Dispensatory*, that "prejudice, together with the unquestionable energy of Quinia as a remedy, has led to the other alkaloid, Cinchonia, being overlooked in practice. The equally strong prepossessions, however, which were long entertained in favour of Crown bark as a febrifuge and stomachic, though it contains but little Quinia, or perhaps none at all, and the proofs which have been given of the great efficacy of the gray, or Huanuco bark, would justify the inference that Cinchonia, too, is eminently active. Accordingly, trials made with it by Dr. Bardsley, in England, as well as various practitioners of credit in France, Germany and Italy, seem to leave little doubt that it is scarcely inferior to Quinia in the treatment of intermittent; and some continental writers even maintain that, while equally energetic, it is likewise even less likely to disorder the stomach in large doses." In like manner, in the *United States Dispensatory*, Dr. Wood states: "There is little doubt, however, that *Cinchonia* possesses febrifuge properties little, if at all, inferior to those of Quinia; and should the source of the latter begin to fail, the pale bark would come into more extensive use for the preparation of the former."—*On the use*

of *Bebeerine and Cinchonia*, by Dr. Wm. Pepper : *American Journal Med. Sciences*, Jan. 1853. So likewise in *Pereira's Materia Medica and Therapeutics*, a work of the highest authority:—

“ If we take into consideration the similarity of chemical properties of Cinchonia and Quinia, we are led to suspect analogy of physiological effects. When they were in the first instance submitted to examination, Cinchonia and its salts were thought, principally on the evidence of Chomel, to be much inferior in activity to Quinia and its salts. But the subsequent observations of Dufour, Petroz, Potier, Bally, Nieuwenhuiss, Mariani, Bleyne, and others, have appeared to prove that the sulphates of these alkaloids may be substituted for each other. Nay, Bally gives the preference to the Sulphate of Cinchonia, on the ground that it is less irritating than the Sulphate of Quinia. That Cinchonia is as active as Quinia might have been anticipated, *a priori*, when we recollect that those barks in which Cinchonia is the predominant principle, were the first which were celebrated as Therapeutic agents.

“ As Cinchonia and its salts are less bitter than Quinia and its salts, we might expect that the former would possess somewhat less medicinal activity than the latter; and this inference is probably correct. Moreover, as Cinchonia and its salts have a more nauseous flavour, and are more allied to that of Sulphate of Magnesia, it might naturally be anticipated that large doses of Sulphate of Cinchonia would be more apt to create nausea and vomiting than like doses of Sulphate of Quinia; and I have been informed by some medical friends that this is in reality the

case. I must confess, however, that I have been unable to verify it. I have extensively used in hospital practice Sulphate of Cinchonia, in doses not exceeding ten grains, and have not met with the nausea and vomiting I expected to have met with. In a case of ague I ordered the patient (a young man) to take ten grain doses of the Sulphates of Quinia, Quinidia, and Cinchonia on separate successive days, every two hours before dinner; that is, the Sulphate of Quinia on one day, the Sulphate of Quinidia on the second, and the Sulphate of Cinchonia on the third day. The case was very carefully watched by one of my clinical clerks, but no difference of effect was discernible. No sickness or vomiting took place. I have found the Sulphate of Cinchonia valuable both as a tonic and febrifuge or antiperiodic."—*Pereira's Mat. Med.* (Philad. 1854), vol. ii., pp. 681-2.

Dr. Pepper, in the memoir already quoted, reports the result of the trials made by him of the Sulphate of Cinchonia at the Pennsylvania Hospital.

In the fifteen cases reported, "the Cinchonia was administered with the most signal success, and fully confirmed the above statements as to its efficacy. In a majority of these the disease had been of many month's duration, and was attended with enlargement of the spleen, and more or less impairment of the general health; yet, notwithstanding these serious difficulties, it was promptly checked at the first effort in eleven of the cases, and in two of these Sulphate of Bebeerine had first been unsuccessfully tried. In only two instances was it necessary to administer the Cinchonia a second time for the arrest of the paroxysms; and of the whole number, as far as it could be

ascertained, but two relapsed, and these were promptly and permanently checked by again resorting to the Cinchonia in full doses." * * "Judging from my experience in former seasons, in similar cases, I am fully convinced that the Cinchonia proved quite as efficacious as Quinia, and occasionally, indeed, it appeared to be even more prompt." Dr. Pepper adds "that in several cases of neuralgia and intermittent fever, which have fallen under my observation in private practice, the Cinchonia has succeeded after the failure of the Quinia in similar doses."

Dr. Kenderdine, the Resident Physician of the Hospital of the Protestant Episcopal Church, in Philadelphia, in a communication dated 7th. October 1854, and addressed to Powers and Weightman, states that he has used the Sulphate of Cinchonia in over three hundred cases of Malarious Fevers of various types. "In these cases the Sulphate of Cinchonia has been given in the same doses that Sulphate of Quinia would have been, viz., 15 to 18 grains, the chills checked, the periodical character of the disease broken up, but the tendency of the disease to return at weekly or bi-weekly periods has been about the same as when the Sulphate of Quinine had been used."

The evidence thus brought together proves conclusively that the Sulphate of Cinchonia is a remedy for intermittent fever, fully as efficacious as the Sulphate of Quinia. There are probably the same shades of difference in their medical properties as in the gray and yellow barks in which they severally exist, giving the preference sometimes to the one and sometimes to the other.

Yet why, if the Sulphate of Quinia answers all the

purposes for which the Cinchonas have become celebrated, why need the Cinchonina be used at all? There would perhaps be no sufficient reason for wishing to introduce it, were the expense of administering the two alkaloids the same.

But the barks which are now collected in South America, and which have to be used in the preparation of these alkaloids, yield Cinchonina as well as Quinia, and the small demand for the former causes it to be offered at a lower price, in order to find sale for it.

“Not only,” as Dr. Pepper remarks, “is Cinchonina an efficient remedy, but it derives additional importance from the fact that at the present time it can be supplied at far less than half the price of Quinia. The poor are now in a measure debarred from the use of this last-named remedy, owing to its high cost, but this evil could, in a great degree, be obviated by the general introduction of Cinchonina.”

In the quotation from Pereira's *Materia Medica*, given above, a third alkaloid of the Cinchonas, the Quinidia, is mentioned. It was discovered and its properties investigated in 1848. It exists in the pale Loxa and Lima Barks, and the gray Huanuco Barks, along with the other alkaloids. The barks which are now used for the manufacture of Quinia do not contain it in very appreciable quantities, so that whatever may be the case hereafter, its properties are not now a matter of much practical interest.

The composition of the Quinidia closely resembles that of the other cinchonic alkaloids. They are all, probably, oxides of the same organic base.

Cinchonina is almost insoluble in ether and in cold

water, and Quinidia is much less soluble in them both than Quinia.

The Sulphate of Cinchonia is soluble in about 54 parts of cold water, that of Quinidia in about 130 parts, and that of Quinia in about 140 parts. When a solution of the sulphate of these alkaloids is mixed, first with chlorine water, and then with ammonia, the Sulphate of Quinia becomes of an emerald green colour; the Sulphate of Quinidia either remains unchanged or yields a white precipitate, and the Sulphate of Cinchonia becomes purplish, and yields a white precipitate.

The Sulphate of Quinia was first successfully prepared in America in 1823; and Farr and Kunzi, the founders of the present house of Powers and Weightman, soon became its largest manufacturers. They early discovered that as in the refining of sugar there is always a portion so combined with resinous proximate principles as to be uncrystalized, there remained in this new manufacture, after all the Quinia they could obtain was separated, a viscid dark brown liquid, evidently very rich in the active principle of the Cinchona. They evaporated this liquid to dryness, and John Farr furnished the writer of this memoir with specimens for the purpose of trial by his medical friends. It was first prescribed by Dr. Samuel Emlen, in doses of two grains, with entire success. Drs. Parrish and Wood next tried it with the same result; and from that time "*the Extract of Quinine*," as it was then called among us, came into use, and has ever since been extensively prescribed in Dispensary practice, as a cheap and perfectly reliable anti-periodic.

This amorphous residue has been the subject of much investigation in Europe. Sertuerner announced in 1829, that he had discovered it to consist chiefly of a new alkaloid which he called Chinoidine, and which he regarded as a more valuable anti-febrile than the Quinia itself.

Professor Liebig more recently obtained samples of this Chinoidine or Quinoidine from several of the best manufacturing chemists of Germany, and after carefully separating the foreign matters which they contained, ascertained its composition to be identical with that of Quinia. He says that the inference from his experiments is irresistible. "Some doubts," says Pereira, (1853) "however, still exist as to the real nature of the so-called amorphous Quinia. Roder declares (1848) that it is merely ordinary quinia combined with a resin; while Van Heijningen (1850) resolved the so-called quinoidine into ordinary quinia, cinchonia, quinidia, and a resinous substance."

In 1846 a series of preparations known as Bullock's "Purified Chinoidine," Bullock's "Amorphous Quinine," Bullock's "Basic Extract of Bark," were patented in England, and were highly recommended. They were obtained from the amorphous residue of the manufacture of Sulphate of Quinia; but the cost of preparation was not compensated by any great superiority over the cheaper purified Chinoidine of our best manufacturers over old "Extract of Quinine."

"The uncrystalline substance derived from Quinoidine bears exactly the same relation to ordinary quinine that uncrystalline sugar (barley-sugar) bears to crystalline (sugar candy.) Both yield the same pro-

ducts of decomposition; both have the same atomic weight, and identically the same composition; they differ only in form; in one word, the one is crystalline, the other, *amorphous*.

“I deem this to be an important discovery, when we consider the high price of Quinine, the possibility of a check to the supply of Cinchona bark from the countries producing it, and the amount of the crude Quinoidine which has accumulated since the manufacture of Sulphate of Quinine was commenced. Quinine, indeed, seems to be absolutely indispensable for the treatment of diseases; the progress of civilization in modern times has depended, far more than has been conceived, upon the discovery of a remedy for the fevers which prevail where tillage is imperfect, and in new and unbroken soils.

“This chemical investigation has thrown an interesting light upon the testimonies borne to the efficacy of Quiniodine in the treatment of fever, and the highest encomiums have been passed upon it; but the commercial specimens have differed very much in value; while some have consisted nearly altogether of amorphous Quinine, others have contained only a small per centage.

“It is necessary that the amorphous Quinine should be separated from all admixtures and impurities, and prescribed in its pure state. There can be no doubt but the same substance will produce the same effect on the animal organism, whether exhibited in a crystalline or an amorphous state. The system, as we may say, makes no difference in such a case. As I have already observed, the mystery about Quinoidine is completely solved by the discovery that it usually

contains a very large per centage of pure quinine in an amorphous state.

“ In a commercial point of view, it is certainly a matter of great importance that we should be able to judge by the mere external appearance of a remedy of its purity, and, consequently, how far we may rely upon its efficacy. This is thought to be the case with the Crystalline Sulphate of Quinine, whilst the non-crystalline form of Quinoidine has probably led to a disregard of the evidence of its usefulness, even more than the fact of its being, as usually sold, an admixture of various substances. But with respect to the mere amorphous form, when the Quinine is separated from all its adhering impurities, it is in the same case with opium, castor; and many more of the most efficient remedies which we possess, particularly with the extracts of our Pharmacopœias. It is necessary to be assured of their purity before we employ them, but their amorphous form does not prevent their use. In many of these cases, indeed, having no direct or ready way of testing them, we rely solely upon the honorable character of the merchant and dealer; but we have a completely satisfactory test for the purity of amorphous Quinine. Few medicinal agents afford so ready a means of distinguishing them, and detecting admixtures, as the organic alkaloids; but if these tests are not employed, it is as easy to be deceived in purchasing Chrystalline Sulphate of Quinine as the amorphous.”

There is additional evidence of the value of this latter preparation, in an article “on Quinoidine in the treatment of Intermittent Fever, by J. Da Costa, M. D.,” in the Medical Examiner for May 1855.

The Quinoidine used by Dr. Da Costa was from the manufactory of Powers and Weightman. He gives the result of fifty-three cases in which he administered it. He says that the therapeutical effects of Quinoidine, as far as he has observed them, "are very nearly those of the ordinary Sulphate of Quinia. In doses two-thirds larger than those of the latter, he succeeded perfectly in checking intermittent fever; but it was never noted to give rise to the head-ache, nor the ringing and buzzing in the ears, nor to the sickness at the stomach, which so frequently attend the ministration of the Sulphate of Quinia, or of the other ordinary preparations of bark. It was sometimes given in doses of 40 grains, without the slightest inconvenience to the patient resulting from it, and in no case, with the exception of one, did it fail in checking the periodical returns of the paroxysms. In a few instances, indeed, it proved successful where Sulphate of Quinia had been previously administered without result. As a tonic, it seems to present the same advantages as any other of the preparations of bark. Age does not constitute an objection to its use, for it was employed with equal advantage in the very young and the very old."

"Of the 53 cases cited, in many of whom the disease was of long standing, the chills were arrested in 49 cases by the first administration of the medicine; only four required a repetition of the dose. In 10 cases the disease returned, which, although it may seem a large proportion of relapses, was not in reality so, when we consider the well known tendency of intermittent fever to return, and the fact that, in many of the cases, no medicine, for reasons above

stated,* was given after the first arrest of the chill. In conclusion, the writer can state as his honest belief, that Quinoidine possesses anti-periodic qualities, which if not superior, are certainly not inferior to the Sulphate of Quinia or Cinchonia, whilst he thinks it preferable to these, from the absence of bitter taste, from its being less liable to affect the head or stomach of the patient, and from its comparatively low price."

The objection that the amorphous character of the Quinoidine renders it liable to adulteration, applies alike to every amorphous article of the *Materia Medica*. It can only be met by the assertion that establishments of unquestionable integrity, such as our best manufacturing chemists and wholesale and retail druggists, are above all suspicion of wilful adulteration; that the packages containing these preparations always bear the name of the manufacturer, and that a fraud would be almost immediately followed by detection and exposure.

* The reason given is that "as patients when relieved are not always willing to return to a public Institution, it was sometimes impossible to persevere with the treatment, and the disease then generally re-appeared after the lapse of a week or two."

The annexed paper on the cheaper Alkaloids of the Cinchona[✓] has been written, at our request, by our friend Daniel B. Smith, Esq., of Germantown, for many years President of the Philadelphia College of Pharmacy. We would only add, that accounts which we are constantly receiving in relation to the medicinal efficacy of Sulphate of Cinchonia and Chinoidine, fully corroborate the favorable views expressed by the authors whom he has quoted.

POWERS & WEIGHTMAN.

Philadelphia, September 1855.

